Applicant's Invention

Applicant's invention, as set forth in Group II, Claims 14-54, is directed to drug carriers, drug carrier complexes, drug carrier compositions and pharmaceutical formulations. Drug carrier complexes set forth in Claims 28-33 and 35, include a single-stranded nucleotide, a drug, and a polymer. In one embodiment, as set forth in Claim 28, the drug carrier complex includes a single-stranded nucleotide, a drug reversibly associated with the single-stranded nucleotide, and a polymer associated with the single-stranded nucleotide or drug. In another embodiment, set forth in Claim 31, the drug carrier complex includes a single-stranded nucleotide, an oligomer associated with the single-stranded nucleotide and a drug reversibly associated with the oligomer or the single-stranded nucleotide. Claim 35 sets forth a drug carrier complex that includes an oligomer, a single-stranded nucleotide entrapped by the oligomer, and a drug reversibly associated with the single-stranded nucleotide. In all cases, and as set forth in the specification at page 10, lines 5-9, the drug carrier complex includes a nucleotide strand and a drug reversibly associated, directly or indirectly, with a single-stranded nucleotide.

> In one embodiment, a drug-carrier complex is formed by combining at least one nucleotide strand with a drug. The drug is in reversible association with the nucleotide component to form the drug-carrier complex. Thus, a "drug-carrier complex," as used herein, (also referred to as a "nucleotide-carrier complex") refers to at least one nucleotide strand and a drug that are in reversible association with each other.

(Emphasis added.)

Further, the terms "associate," "association," and "associable," as used in the specification are defined at page 10, lines 10-28. Examples of "reversible association" include electrostatic bonding, hydrogen bonding, van der Waals forces, ionic interaction and donor/acceptor bonding.

Another embodiment of the invention includes drug carriers. As set forth in Claim 14, a drug carrier includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one milligram per liter at 25° C. As set forth in Claim 23, the drug carrier includes a double-stranded nucleotide and a oligomer component covalently bonded to at

least one strand of the double-stranded nucleotide. Claim 34 is directed to a drug carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide. None of the claimed "drug carriers" include a "drug" as that term is defined in Applicant's specification. Rather, drug carriers are the drug-carrying component of "drug carrier complexes." As set forth in the specification at page 13, lines 11-16:

> The term "nucleotide component" refers to the drug-binding (drug carrying) component of the drug-carrier complexes of this invention. The drug-binding component comprises at least one nucleotide strand. The nucleotide component may include, or be further associated with, other components (e.g., polymers, oligomers, ligands) to form [a] drug carrier, a drug delivery system, or a drug-laden implant. In one embodiment, the nucleotide strand is an oligonucleotide strand.

As shown at page 13, lines 28 through page 14, line 9, a "drug," as that term is employed by Applicant, refers to therapeutic and diagnostic compounds:

> The term "drug" is used herein interchangeably with the term "drug component." In one embodiment, the drug of the pharmaceutical formulation is a therapeutic drug. The term "therapeutic," when referring to a drug used in the invention, refers to a drug used to treat, remediate or cure a disorder or a disease (e.g., hereditary diseases, viral diseases such as AIDS, cancer). In another embodiment, the drug of the pharmaceutical formulation is a diagnostic drug (e.g., a radioactive diagnostic drug, a fluorescent diagnostic drug, a paramagnetic diagnostic drug, superparamagnetic diagnostic drug, an x-ray dense diagnostic drug or an electron-dense diagnostic drug). The term "diagnostic," when referring to a drug employed in the invention, refers to a drug employed to determine the nature or extent of a disease, or employed to confirm the presence of a disorder or a disease.

Claims 36-54 are directed to drug carrier compositions and pharmaceutical formulations. Drug carrier compositions, as set forth in Claims 36 and 37 include a nucleotide carrier component and a drug component. Claim 38, directed to a pharmaceutical formulation, includes

a nucleotide carrier component and a drug in reversible association with the nucleotide carrier component.

Advantages of Applicant's Invention

Applicant's claimed nucleotide-based drug delivery systems have many advantages. For example, they can transfer drugs in chemically unmodified form, and can reabsorb the released drug. By employing a reversible drug association, the drug delivery systems of this invention are able to reincorporate the released drug. Thus, drug behavior in the tissues may remain dependent on the drug release system for as long as the latter remains functional, which offers the possibility of new opportunities in regulation of pharmacokinetics and pharmacodynamics. In a clinical setting, this is expected to result in better biological functionality and broader safety margins of pharmaceutical formulations and devices.

Also, stability and release rates of drug-carrier complexes of the invention can be controlled within a broad range, thereby providing the opportunity to design products in accordance with specific clinical objectives. Further, release of drugs by the drug-carrier complexes of the invention does not require interactions with enzymes, cells or other factors, thereby making the drug-carrier complexes more independent of the organism and tissue state. Complexes of the invention can be designed to exploit specific conditions of an organism or tissue state, such as pH or enzyme content. In addition, the components of the drug-carrier complexes of the invention can be made of close analogs of natural components of biological systems which are known to be completely biodegradable and non-toxic.

Other specific advantages of the invention include the possibility of steric protection against carrier clearance and drug inactivation. Also, the drug-carrier complexes of the invention generally have no problems relevant to intramolecular or intermolecular association of drug molecules. Further, methods of forming and processing the drug-carrier complexes of the invention are readily scalable. Also, drug-carrier complexes are lyophilizable, and all components of the complexes can be stable in the presence of air. Further, no toxic surfactants are employed, and the size of the complex is generally stable and does not depend on conditions and concentration. Drug release rate within an organism generally does not depend on highly

variable adsorption forces. Ultrafiltration typically does not affect size and structure of the drug-carrier complexes.

Amendments to the Claims

Claim 19 has been amended to delete the phrase "and derivatives thereof." Claim 34 has been amended to correct a grammatical error identified by the Examiner. The correction of Claim 34 is self-evident. The amendments to Claim 19 and 34 do not add any new matter.

Elections/Restriction

In Paper No. 11, the Examiner made a Restriction Requirement to one of seven groups of claims. The basis for the Examiner's restriction of the claims into Groups I through VII, as unrelated inventions, was set forth at pages 3 through 5 of the Restriction Requirement. As required by the Manual of Patenting Examining Procedure (MPEP), at § 814 and § 816, the Examiner provided a short description of the total extent of the invention claimed in each group, and specified the type or relationship of each group. Further, the particular reasons relied upon by the Examiner for holding that Groups I through VII are distinct inventions was also set forth. For purposes of examination, Applicant elected Group II (Claims 14-54), without traverse.

In addition, the Examiner required that the Applicant select, within Groups I-V, one drug, one carrier and, either one polymer or a specific combination of two polymers, or an oligomer or a specific combination of oligomers. The Examiner did not, however, provide a basis for further dividing the claims of Applicant's elected group, Group II. The only statements in support of the additional requirement were that Applicant should select from one of the following inventions within Groups I-V," and that the "claims in each group will be examined according to the limitations of the elected invention since some claims were found to be generic to patentably distinct groups."

Because no basis was provided by the Examiner for considering any further grouping of claims according to selection of one drug, one carrier and one polymer/oligomer combination to be patentably distinct, Applicant understood that the selection of one drug, one carrier and one polymer oligomer or a combination thereof to be an election of species, whereby the search and

examination would be broadened beyond the scope of the species in the event a reference could not be identified disclosing Applicant's elected species. Further, because Applicant understood that the selection of a combination of one drug, one carrier and one polymer/oligomer combination was a selection of a species, Applicant did not traverse that portion of the Restriction Requirement.

Applicant now understands, based on comments made in Paper No. 14, that the Examiner intended to make a further restriction requirement within Groups I-V, based on the drug, carrier and polymer/oligomer combination selected by Applicant. Further, Applicant now understands that the Examiner considers certain claims within Group II, the group which was elected by Applicant for prosecution, to be permanently withdrawn from consideration during prosecution of this application as being drawn to a non-elected invention.

According to § 808.02 of the Manual of Patent Examination Procedure (MPEP), where related inventions as claimed are considered distinct by the Examiner, reasons must be established for insisting upon the restriction:

> Where, as disclosed in the application, the several inventions claimed are related, and such related inventions are not patentably distinct as claimed, restriction under 35 U.S.C. § 121 is never proper (MPEP § 806.05). If applicant optionally restricts, double patenting may be held.
>
> Where the related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c)-§ 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following:
>
> (A) **Separate classification thereof:** This shows that each distinct subject has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Patents need not be cited to show separate classification.
>
> (B) **A separate status in the art when they are classifiable together:** Even though they are classified together, each subject can be shown to have formed a separate subject for inventive effort when an explanation indicates a recognition of separate inventive effort by inventors. Separate status in the art may be shown by citing patents

> which are evidence of such separate status, and also of a separate field of search.
>
> (C) **A different filed of search:** Where it is necessary to search for one of the distinct subjects in places where no pertinent art to the other subject exists, a different field of search is shown, even through the two are classified together. The indicated different field of search must in fact be pertinent to the type of subject matter covered by the claims. Patents need not be cited to show different fields of search.
>
> Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons exist for dividing among related inventions.

(Emphasis in original.)

Nowhere did the Examiner state that the several inventions embraced by the drug, carrier and polymer/oligomer combinations proposed within Groups I-V were unrelated, or if related, distinct under the criteria of MPEP § 806.05 (c) through § 806.05 (i), as is required by MPEP § 808.02. Specifically, there is no indication that the "patentably distinct groups" referred to by the Examiner in the last sentence of paragraph seven (7) on page 3 of Paper No. 11, refer to each of the various combinations of individually-listed drug-carrier and polymer/oligomer choices provided by the Examiner. Further, no basis was provided by the Examiner as to why each of those combinations would be patentably distinct, or why subgroups of claims within Group II would be patentably distinct from each other.

Applicant respectfully requests rejoinder of the claims within Group II in the event that the Examiner does not identify the combination of an intercalator as the drug, a double-stranded nucleotide as the carrier and a polyacetal as the polymer, as components in a drug carrier complex that is disclosed in a single reference. For example, the Examiner stated that Claim 18 is withdrawn from further consideration pursuant to 37 C.F.R § 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Contrary to the Examiner's statement, Claim 18 is dependent from Claim 17, which was not withdrawn from consideration. Therefore, Claim 17 is generic to Claim 18, and Claim 18 should be rejoined in the event the species selected by Applicant is not identified in the prior art. Further, Applicant respectfully requests rejoinder of the remaining claims within Group II, the Examiner not having

made clear that the subject-matter of the remaining withdrawn claims of Group II are unrelated or otherwise patentably distinct, and not having provided the necessary supporting basis for such a conclusion.

Rejection of Claims under 37 U.S.C § 112, Second Paragraph

Claims 16, 19, 22 and 34 stand rejected under 37 C.F.R § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject-matter which Applicant regards as the invention. In particular, the Examiner requested clarification with respect to "cross-linking" of the polymer component in Claim 16. The Examiner also stated that the meets and bounds of "derivatives thereof" of Claim 19 are unclear, as are the meets and bounds of the phrase "chemically distinct polymers" of Claim 22. The Examiner also requested correction of a grammatical error in Claim 34.

With respect to the term "cross-linked," the only reference in the specification to cross-linking is that of cross-linking the polymer component itself, i.e., intermolecular cross-linking. All other bonding referenced in the specification, such as that between the drug and the nucleotide, between the nucleotide and the polymer, or between the polymer and the drug, whether covalent or "reversible," is described as an "association." The term "association" is defined at page 10, line 10 through page 11, line 6. Reference to cross-linking, such as at page 18, line 6, is only with respect to the polymer component and not with respect to a combination of the polymer and any other component of the drug-carrier or drug-carrier complex. Therefore, "cross-linking" as referenced in the specification is only intermolecular cross-linking of the polymer component of the claimed invention.

Claim 19 has been amended to delete the phrase "derivatives thereof." An example of a polyacetal selected from the group consisting of poly(hydroxymethylethylene hydroxymethylformal) of Claim 19, as amended, is shown in Example 8, at page 37, line 26, and Example 9, at page 38, lines 10-12.

With respect to Claim 22, examples of "chemically distinct polymers" are set forth at page 18, lines 9-11. Claim 22 meets the requirements of 35 U.S.C. § 112, second paragraph, without amendment.

Claim 34 has been amended, as required by the Examiner. As amended, Claim 34 is grammatically correct as an independent claim and meets the requirements of 35 U.S.C. § 112, paragraph 3.

Rejection of Claims under U.S.C. § 112, First Paragraph

Claims 19 and 22 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject-matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention.

In particular, the Examiner stated that "the specification does not describe elements which are essential to the genera comprising chemically distinct polyacetal polymers, or comprising derivatives of the polyacetal polymer, poly(hydroxymethylethylene hydroxymethylformal)." The Examiner further stated "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genera claimed and, thus, Applicant was not in possession of the claimed genera."

Claim 19 has been amended to delete reference to "derivatives." One skilled in the art would recognize a poly(hydroxymethylethylene hydroxymethylformal) compound. Examples of poly(hyroxymethylethtlene hydroxymethylformal), within the scope of Claim 19 as amended, are set forth in Example 8, at page 37, lines 25-27 and at Example 9, at page 38, lines 10-12. Therefore, the specification provides description of a representative number of species of the genera set forth in Claim 19. Therefore, the specification meets the requirements of 35 U.S.C. § 112, first paragraph, as applied to Claim 19, as amended.

With respect to Claim 22, examples of chemically-distinct polymers are set forth in the specification, at page 18, lines 9-11. The specification supports the scope of Claim 22. Therefore, the requirements of 35 U.S.C. § 112, first paragraph, are met as applied to Claim 22.

Rejections of Claims under 35 U.S.C. § 102(a) or (e)

Claims 28, 30 and 34 stand rejected under 35 U.S.C. § 102(a) or (e) as being anticipated by U.S. 5,817,343, issued to Burke (hereinafter "Burke"). In particular, the Examiner stated that Burke teaches diagnostic, therapeutic or prophylactic drug-carrier compositions comprising a

biocompatible, polyacetal polymeric component, and comprising double-stranded or single-stranded polynucleotides, and which polymer component is optionally heterogenous or homogenous (i.e., optionally comprising at least two chemically-distinct polymers), which drug-carrier complex comprises reversible associations (i.e., salt or ionic bridges, hydrogen bonding) between the polymer, nucleic acid and drug components. The Examiner specifically recited, in addition to the entire document, Col. 2, line 44 through Col. 5, line 11; Col. 6, line 64 through Col. 7, line 16 and Claims 3 and 11.

Burke is directed to polymer/drug microparticles. The polymer can be a biocompatible polymer, such as poly(lactic acid-co-glycolic acid). The drug can be a labile drug, such as a protein, or a polynucleotide. The term "drug," as defined by Burke, is set forth at Col. 4, line 57 through Col. 5, line 3:"

> As used herein the term "drug"refers to an agent, or its pharmaceutically acceptable salt, which possesses therapeutic, prophylactic or diagnostic properties in vivo. Examples of suitable therapeutic or prophylactic agents which can be labile drugs, include, for example, proteins such as immunoglobulin-like proteins, anitbodies, cytokines (e.g., lymphokines, monokines, chemokines), interleukins, interferons, erythropoietin (also referred to herein as "EPO"), nucleases, tumor necrosis factor, colony stimulating factors, insulin, enzymes, tumor suppressors, hormones (e.g., growth hormone and adrenocorticotrophic hormone), antigens (e.g., bacterial and viral antigens), growth factors, peptides, polypeptides, and polynucleotides, such as antisense molecules.

Applicant's invention, as claimed in independent Claim 28, is a drug-carrier complex that includes "a single-stranded nucleotide"; "a drug reversibly associated with the single-stranded nucleotide"; and "a polymer associated with the single-stranded nucleotide or the drug." Claim 30 is dependent from Claim 28 and adds the further limitation that the polymer is associated with drug. Claim 34 is directed to a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide.

There no disclosure or suggestion in Burke of a drug-carrier complex that includes a single-stranded nucleotide, a drug reversibly associated with a single-stranded nucleotide and a polymer associated with the single-stranded nucleotide or the drug, as claimed by Applicant in Claim 28. Specifically, there is no disclosure in Burke of a single-stranded nucleotide component distinct from the drug and polymer components of the disclosed polymers/drug matrix particles described in Burke. Rather, the polynucleotides disclosed in Burke are examples of labile drugs which, by definition, possess therapeutic, prophylactic or diagnostic properties *in vivo*. There is no disclosure of the presence of a single-stranded nucleotide component of the polymer/drug matrix particles, other than those which are drugs. Therefore, Burke does not disclose Applicant's invention, as set forth in Claim 28. Claim 30 is dependent from Claim 28. Therefore, Burke also does not disclose the subject matter of Applicant's Claim 30.

Applicant's Claim 34 is directed to a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide. As discussed above, Applicant's claimed drug-carrier, including a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, is distinct from a "drug" component of a "drug-carrier complex."

There is no disclosure or suggestion in Burke of a combination of a polynucleotide and a polymer wherein the polynucleotide is not also a drug. Therefore, Burke does not disclose Applicant's claimed drug-carrier, as set forth in Claim 34 of the instant application.

The subject matter of Claims 28, 30 and 34, meet the requirements of 35 U.S.C. § 102 in view of Burke.

Rejection of Claims under 35 U.S.C. § 103

Claims 14-17, 20-22, 28-30 and 34, stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Burke, as applied to Claims 28, 30 and 34, and further in view of the combination of Matysiak, *et al.*, "Acetal Oligonucleotide Conjugates in Antisense Strategy," *Nucleosides and Nucleotides*, 16(5&6):855-861 (1997) (herein after "Matysiak, *et al.*"), U.S. 6,057,431, issued to Ishihara, *et al.*, (herein after "Ishihara, *et al.*) and Gao, Q. *et al.*, "Drug-induced DNA repair: X-ray structure of a DNA-ditercalinium complex," *Proc. Natl. Acad. Sci. USA*, 88:2422-2426, March 1991 (herein after "Gao, *et al.*"). In particular, the Examiner stated

that it would have been obvious to one of ordinary skill in the art to design and utilize drug-carriers comprising a nucleotide component and in a biocompatible polyacetal component because such drug-carrier complexes have been successfully designed and utilized for target cell delivery of various agents including for labile drug delivery, as taught previously by Burke. Further, the Examiner stated:

> One of ordinary skill in the art would have expected that biologically compatible nucleotide conjugates are obtained utilizing acetal-containing polymers because nucleotide conjugation to various moieties utilizing acetyl groups have been taught previously by Matysiak, *et al.*, and covalently-linked nucleotide conjugates have been shown to have enhanced biological stability in appropriate biological contexts compared to non-conjugated drug-carriers, as taught previously by Ishihara *et al.*

Also, the Examiner stated that:

> One of ordinary skill in the art would have been motivated to utilize intercalating agents for therapeutic or diagnostic purposes because intercalating agents are known to be successfully delivered to target cells as bioconjugates, as taught previously by Ishihara, *et al.*

The Examiner also stated that "the bis-intercalating agent, ditercalinium, has been used as an anticancer drug by inducing DNA repair systems when delivered to target cells, as taught previously by Gao, *et al.*"

Applicant's Claims 14 through 22 are directed to a drug-carrier that includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/liter at 25°C. Claims 28-30 are directed to a drug-carrier complex that includes a single-stranded nucleotide, a drug reversibly associated with a single-stranded nucleotide, and a polymer associated with a single-stranded nucleotide or the drug. Claim 34 is directed to a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide.

As discussed above, there is no disclosure or suggestion in Burke of a drug-carrier complex that includes a single-stranded nucleotide, a drug reversibly associated with the single-stranded nucleotide, and a polymer associated with the single-stranded nucleotide or the drug. As also discussed above, there is no disclosure or suggestion in Burke of a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide. Further, there is no disclosure or suggestion in Burke of a drug-carrier, as set forth in Claim 14, that includes a double-stranded nucleotide, and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer has an aqueous solubility of at least one mg/liter 25°C. As discussed above, there is no disclosure or suggestion in Burke of a drug-carrier or of a drug-carrier complex that includes a polynucleotide component that is not itself a "drug," as that term is defined by Applicant at page 13, line 28 through page 14, line 25.

Matysiak, *et al.*, teach a method to enhance cellular uptake of antisense oligonucleotides or their analogs by linking them with derivatized cholesteryl-acetals.

Matysiak, *et al.* do not remedy the deficiencies of Burke. Specifically, there is no disclosure or suggestion in Burke, or Matysiak, *et al.*, taken either separately or in combination of a drug-carrier that includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/l at 25°C, as set forth in Applicant's Claims 14-17 and 20-22. Further, there is no disclosure or suggestion in either Burke or Matysiak, *et al.*, taken either separately or in combination of a drug-carrier complex that includes a single-stranded nucleotide, a drug reversibly associated with the single-stranded nucleotide, and a polymer associated with the single-stranded nucleotide or the drug, as set forth in Applicant's Claims 28-30. Also, there is no disclosure or suggestion in Burke or Matysiak, *et al.*, of a drug-carrier that includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide as set forth in Applicant's Claim 34. Therefore, neither Burke or Matysiak, *et al.*, taken either separately, or in combination, disclose or suggest Applicant's claimed invention.

Ishihara, *et al.*, teach amidite derivatives and oligonucleotide derivatives. More specifically, complexes of saccharides and oligonucleotides are disclosed. The saccharide

component is employed as a means for delivery of the oligonucleotide in order to affect expression in a cell, such as by delivering an antisense oligonucleotide to suppress expression of a specific gene of a targeted organ. In the background portion of Ishihara, *et al.*, referenced by the Examiner, other combinations of oligonucleotides and compounds, including intercalators, are described. In each embodiment in Ishihara, *et al.*, the oligonucleotide is a "drug," as that term is defined by Applicant in the instant application.

As with Matysiak, *et al.* and Burke, there is no disclosure or suggestion in Ishihara, *et al.* of Applicant's claimed drug-carrier or drug-carrier complex, as set forth in pending Claims 14-17, 20-22, 28-30 and 34. Specifically, there is no disclosure or suggestion in Burke, Matysiak, *et al.* or Ishihara, *et al.*, taken either separately or in combination, of a drug-carrier or drug-carrier complex that includes either a single- or double-stranded nucleotide that is a component of a drug-carrier, as opposed to a drug-carrier complex, or as a distinct non-drug component of a drug-carrier complex. Therefore, Applicant's claimed invention is not obvious in view of any of these references, taken either separately or in combination.

Gao, *et al.*, teach combination of a synthetic anticancer drug, ditercalinium, with DNA in a non-covalent complex. The non-covalent DNA-ditercalinium complexes are incorrectly recognized by a uvrABC repair system in procaryotes as covalent lesions on DNA, thereby affecting cellular repair systems of the procaryote.

As with Matysiak, *et al.*, Burke, and Ishihara, *et al.*, there is no disclosure or suggestion in Gao, *et al.* of the subject matter of Applicant's drug-carrier, as set forth in Claims 14-17 and 20-22, which includes a double-stranded nucleotide and a polymer component covalently bonded to at least one strand of the double-stranded nucleotide, wherein the polymer component has an aqueous solubility of at least one mg/liter at 25°C. Gao, *et al.*, also does not remedy the deficiencies of Burke, Matysisak, *et al.* or Ishihara, *et al.*, in that none of these references, taken either separately or in combination, disclose or suggest a drug-carrier complex, as set forth in Applicant's Claims 28-30, wherein the drug-carrier complex includes a single-stranded nucleotide, a drug reversibly associated with the single-stranded nucleotide, and a polymer associated with a single-stranded nucleotide or the drug. Also, none of these references, taken either separately or in combination, disclose or suggest a drug-carrier, distinct from a drug-carrier

complex, when the drug-carrier includes a single-stranded nucleotide and at least two polymers associated with the single-stranded nucleotide, as in Applicant's Claim 34.

Specifically, as with Burke, Matysiak, *et al.* and Ishihara, *et al.*, there is no disclosure or suggestion that the DNA component acts as a "drug" as that term is defined by the instant application. As stated by Gao, *et al.*, at page 2425:

> The diversity of the covalent damage excised by uvrABC suggests that the DNA distortions are recognized by uvrABC rather than the intrinsic structural motifs of the adducts . . . . To account for uvrABC recognition of such a diverse array of DNA lesions, it has been proposed (1) the uvrABC recognizes DNA kinks and binds to the face of the DNA that does not contain the adduct.

Therefore, as proposed by Gao, *et al.*, the DNA is not the nucleotide component of a drug-carrier that includes a nucleotide and a polymer, as claimed by Applicant. Further, there is no disclosure or suggestion in Gao, *et al.*, of combination of the DNA component with a polymer to thereby form a drug-carrier. Therefore, there also is no disclosure or suggestion of combining a drug-carrier, that includes a nucleotide and a polymer, with a drug that is reversibly associated with a drug-carrier complex. As a consequence, Gao, *et al.*, do not remedy the deficiencies of the other references cited by the Examiner.

Taken separately or in combination, Applicant's claimed invention, as set forth in Claims 14-17, 20-22, 28-30 and 34, meets the requirements of 35 U.S.C. § 103 in view of Burke, Matysiak, *et al.*, Ishihara, *et al.* and Gao, *et al.*, taken either separately or in any combination.

SUMMARY AND CONCLUSIONS

Applicant respectfully requests that the Examiner rejoin all of Claims 14-54 within Group II. Applicant has amended Claims 19 and 34. As amended, Claims 19 and 34 meet the requirements of 35 U.S.C. § 112, second paragraph. Claims 16 and 22 meet the requirements of 35 U.S.C. § 112, second paragraph, without amendment. Claims 19 and 20 (as amended) and 22 meet the requirements of 35 U.S.C. § 112, first paragraph. The subject matter of Claims 28, 30 and 34 meets the requirement of 35 U.S.C. § 102(a) and (e), in view of Burke. Further, Claims

14-17, 20-22, 28-30 and 34 meet the requirements of 35 U.S.C. § 103(a), in view of Burke, Matysiak, *et al*, Ishihara, *et al.* and Gao, *et al.*, taken either separately or in any combination. Therefore, Applicant respectfully requests reconsideration and allowance of the claims under consideration. Applicant further requests examination of the remaining claims of Group II.

If the Examiner feels that a telephone conference would expedite prosecution of this application, she is invited to call Applicants' undersigned Attorney.

Respectfully submitted,
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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R § 1.121(c)(1)(ii)

19. (Amended) The drug carrier of Claim 17, wherein said polyacetal is selected from the group consisting of poly(hydroxymethylethylene hydroxymethylformal) [and derivatives thereof].

34. (Amended) A drug-carrier, comprising:

a) a single-stranded nucleotide; and

b) at least two polymers [are] associated with said single-stranded nucleotide.